Review

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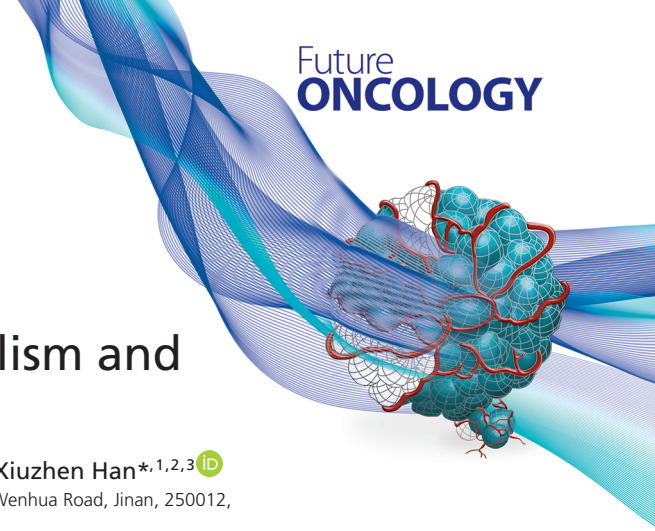

The roles of IDH1 in tumor metabolism and immunity

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IDH1 is a key metabolic enzyme for cellular respiration in the tricarboxylic acid (TCA) cycle that can convert isocitrate into α-ketoglutarate (α-KG) and generate NADPH. The reduction of IDH1 may affect dioxygenase activity and damage the body's detoxification mechanism. Many studies have shown that IDH1 is closely related to the occurrence and development of tumors, and the changes in IDH1 expression levels or gene mutations have appeared in many tumor tissues and produced a series of metabolic and immunity changes at the same time. To better understand the relationship between IDH1 and tumor development, this article reviews the latest advances in IDH1 and tumor metabolism, tumor immunity, IDH1 regulatory mechanisms and IDH1 target inhibitors.

Plain language summary: IDH1 is a key metabolic enzyme for cellular respiration. The changes in IDH1 expression or gene mutations may affect enzyme activity and damage the body's detoxification mechanism. Studies have shown that IDH1 is closely related to the occurrence and development of tumors, and the changes in IDH1 also produced a series of metabolic and immunity changes. To better understand the relationship between IDH1 and tumor development, this article reviews the latest advances in IDH1 and tumor metabolism, tumor immunity, IDH1 regulatory mechanisms and IDH1 target inhibitors.

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Keywords: D-2HG • IDH1 • immunity • metabolism • mutation

Tumors are an abnormal mass of cellular growth in nature. Metabolic disturbance is the main cause of tumors. Abnormal tumor metabolism is often accompanied by changes in the metabolism of multiple substances and enzymes. IDH1 is a key metabolic enzyme for cellular respiration in the tricarboxylic acid (TCA) cycle. IDH1 can catalyze the oxidative decarboxylation of isocitrate to generate α-ketoglutarate (α-KG) [1]. IDH1 not only produces NADPH but also indirectly regulates the metabolism of amino acids and lipids and participate in oxidative stress. Many reports show that IDH1 mutation or protein level changing plays an important role in tumorigenesis and development [2–4]. IDH1 plays an important role in tumor metabolism and tumor immunity. To understand the roles of IDH1 in tumorigenesis and development, this review summarizes the structure, function and regulation of IDH1; the roles of IDH1 in tumor immunity and metabolism; and recent advances in IDH1 targeting inhibitors.

Structure & function of IDH1

IDH1 belongs to the β-decarboxydehydrogenase family. Human cells have three IDH enzymes, NADP-IDH1, NADP-IDH2 and NAD-IDH3 [5]. IDH1 is found in the cytoplasm and peroxisomes, and IDH2 and IDH3 are present in the mitochondria [6].

Structure of IDH1

IDH1 gene is located on chromosome 2q34, with a total length of 18,854 nucleotides, 10 exons and nine introns; the encoded product protein is IDH1 in the TCA cycle. IDH1 consists of two polypeptide chains, each of which consists of 414 amino acids. The structure of IDH1 is summarized (Figure 1). IDH1 starts at the N-terminus and ends at the C-terminus, with a tripeptide alanine-lysine-leucine at the C-terminus [1]. Two IDH1 monomers form a homodimer, and each monomer is composed of three domains: large domains (LD, located at residues 1–103

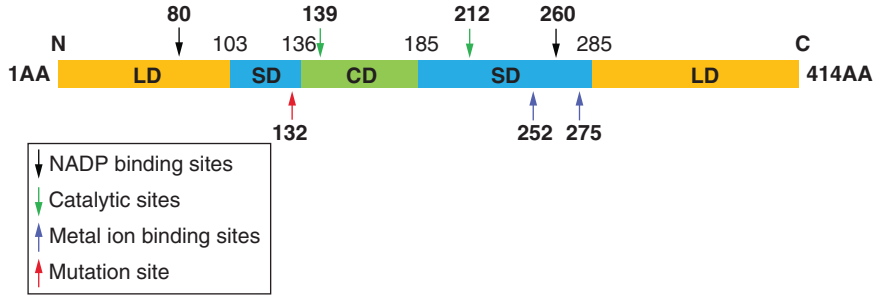

Figure 1. The structure of the IDH1. IDH1 consists of 414 amino acids with important mutation sites, NADP binding sites, catalytic sites and metal ion binding sites.
AA: Amino acid; CD: Clasp domain; LD: Large domain; SD: Small domain.

Table 1. IDH1 and tumors.

Tumors	Effects of IDH1 or 2-HG	Ref.
Early skin tumors	Downregulation of IDH1 promotes tumor growth	[13]
Renal cell carcinoma	Upregulation of IDH1 inhibit tumor growth	[16]
Gliomas	IDH1 upregulation is related to tumor metastasis; patients with IDH1 mutants have longer survival times	[11,17]
Breast cancer	2-HG promotes tumor metastasis	[18]
Cholangiocarcinoma	2-HG promotes tumor growth	[19]
Melanoma	Upregulation of IDH1 inhibit the survival of melanoma cells	[20]
Esophageal carcinoma	IDH1 as a biomarker for the diagnosis and prognosis	[21]
NSCLC	IDH1 as a plasma biomarker for the diagnosis	[22]
Endometrial cancer	IDH1 induces Nrf2 expression and increases chemotherapy sensitivity	[23]
AML	2-HG is related to the prognosis of chemotherapy	[24]

AML: Acute myeloid leukemia; NSCLC: Non-small-cell lung carcinoma.

and 286–414) with Rossmann fold; small domains (SD, located at residues 104–136 and 186–285), forming an α/β sandwich structure [7]; and the clasp domain (CD, located at residues 137–185), which is formed by two antiparallel double strands with β-sheets [7]. The LD and SD are connected by β-folds. In addition, IDH1 also has multiple binding sites, such as NADP binding sites and metal ion binding sites (e.g., Mg^{2+}, Mn^{2+}, Ca^{2+}), which can regulate the active state of IDH1 [7,8].

Functions of IDH1

IDH1 can catalyze isocitrate and simultaneously consume a molecule of $NADP^+$, dehydrogenation to generate a molecule of α-KG, CO_2 and NADPH [9]. The reduced carboxylation of IDH1 is effectively inhibited by NADP+ and isocitrate. IDH1 mutations in the active site are unable to undergo reduced carboxylation of α-KG [10]. The metabolite α-KG is necessary for the activity of dioxygenase in the cytoplasm (including ten-eleven translocation, lysine-specific demethylase 4, prolyl-4-hydroxylase etc.) [11]. IDH1 is also the main source of antioxidant NADPH in the body [12]. Therefore, the reduction of IDH1 function in the cell may damage the body's detoxification mechanism. In addition, IDH1 is also involved in lipid synthesis, glucose metabolism, amino acid utilization and other processes [13–15].

IDH1 & malignant tumors

Many studies have shown that IDH1 is closely related to the occurrence and development of tumors, and the changes in IDH1 expression levels or gene mutations have appeared in many tumor tissues (Table 1). Tyrosine kinase enhances IDH1 activation by phosphorylation with Y42 or Y391 [16]. Mutant and wild-type IDH1 share amplification mechanisms, including distinct tyrosine kinase cascades in cancer [16]. Inhibition of IDH1 tyrosine phosphorylation reduces the production of D-2-hydroxyglutaric acid (D-2HG), thereby inhibiting tumor growth [16].

Wild-type IDH1 & tumor

Studies have shown that the expression of IDH1 decreases during the formation of early skin tumors, and oxidative stress may be an important reason for the downregulation of IDH1 expression [14]. IDH1 is low expressed in renal cell carcinoma, and increased IDH1 can inhibit tumor growth. IDH1 is also related to the hypoxia signaling pathway. IDH1 overexpression significantly inhibits the expression of the HIF pathway and its downstream proteins (TGF-α, VEGF) [17]. Improved survival in non-IDH1-R132H IDH1/2 mutations astrocytoma is associated with increased DNA methylation compared with IDH1-R132H mutations [25].

On the contrary, IDH1 is overexpressed in several lymphomas [7]. IDH1 upregulation is closely related to tumor invasion and metastasis in IDH1 nonmutated glioblastoma [12]. In addition, 2-HG is a chiral molecule with *D*-enantiomer or *L*-enantiomer [18]. Tumor-related IDH1 mutations mainly produce D-2HG [15]. Although there is no IDH1 mutation in many tumors, the oncogenic metabolite D-2HG often accumulates in tumor tissues and cells. For example, oncogene ADHFE1 and MYC signals may be involved in the accumulation of D-2HG in breast tumors [18]. Overexpression of ADHFE1 leads to an increase in D-2HG and epithelial–mesenchymal transition in breast cancer [26].

In addition to changes in the expression level of IDH1, its enzymatic activity will also be affected. Xiang *et al.* found that in some tumor cells, the IDH1-AS1 gene encoding long noncoding RNA enhances the homodimerization of wild-type IDH1, thereby enhancing the activity of IDH1 and delaying tumor progression [27].

Mutant IDH1 & tumor

Metabolites produced by IDH1 mutation participate in a variety of cellular metabolic pathways, such as glucose, amino acids, lipids, glutamine and NADPH [28]. IDH1 mutations can lead to the occurrence of various solid tumors such as glioma [29], chondrosarcoma [19], intrahepatic cholangiocarcinoma [30], colon cancer [20] and melanoma [31]. There are many types of IDH1 mutations, including R132H, R132S, R132C, R132G and R132L. The most important of these is IDH1 (R132H) mutation [28]. R132 mutation is the mutation of the arginine residue at position 132 to histidine or cysteine [28]. The mutant IDH1 has new enzymatic activity, which can reduce α-KG to D-2HG under the action of NADPH. 2-HG can inhibit the activity of a variety of α-KG-dependent hydroxylases, so it has a wide range of effects on cell metabolism, redox homeostasis and epigenetics [32–34]. There are several mechanisms through which IDH1 mutants play a role in tumorigenesis (Figure 2). IDH1 mutants may induce tumorigenesis through the action of oncogenic metabolite 2-HG on signaling pathways [35]. For example, IDH1 mutation in intrahepatic cholangiocarcinoma can transform a-KG into 2-HG [30]. 2-HG inhibits HNF-4α, a major regulator of hepatocyte differentiation, thereby preventing normal differentiation of hepatocytes and leading to increased cell proliferation, promoting the occurrence and progression of intrahepatic cholangiocarcinoma [30]. At the same time, studies have found that IDH1 mutations need to be accompanied by subsequent genetic events, such as TP53 mutations or 1p/19q coding deletion, which ultimately lead to the occurrence of gliomas [36,37].

However, some research has shown that gliomas expressing the mutated IDH1 usually have a better prognosis than wild-type IDH1 gliomas [37]. The reason for this may be that mutated IDH1 affects the tumor microenvironment. In addition, it may also be due to a series of adaptive changes in energy metabolism in gliomas containing IDH1 mutations, which reduces the invasiveness of IDH1 mutant gliomas [2,38]. Grassian *et al.* also found that IDH1 mutations altered TCA cycle and increased reliance on mitochondrial oxidation [39]. Surprisingly, 2-HG has antitumor effects by increasing N^6-methyladenosine (m^6A) RNA modification, thereby reducing the stability of MYC/CEBPA (CCAAT/enhancer-binding protein alpha) transcription and inhibiting the occurrence of tumors [40]. Although IDH1-mutant gliomas may be less malignant, they may also be resistant to certain treatments such as radiotherapy [41].

IDH1 & tumor metabolism

Tumor metabolism has been shown to change the tumor microenvironment. A metabolic disorder is a sign of cancer and promotes tumorigenesis and development [42]. As a key enzyme in metabolism, IDH1 causes a series of changes in the metabolic pathway of tumor cells and further promotes the progress of the tumor (Figure 3). Molecular metabolic imaging demonstrates dysregulation of glucose and lipid metabolism in IDH1-mutant tumor cells [43].

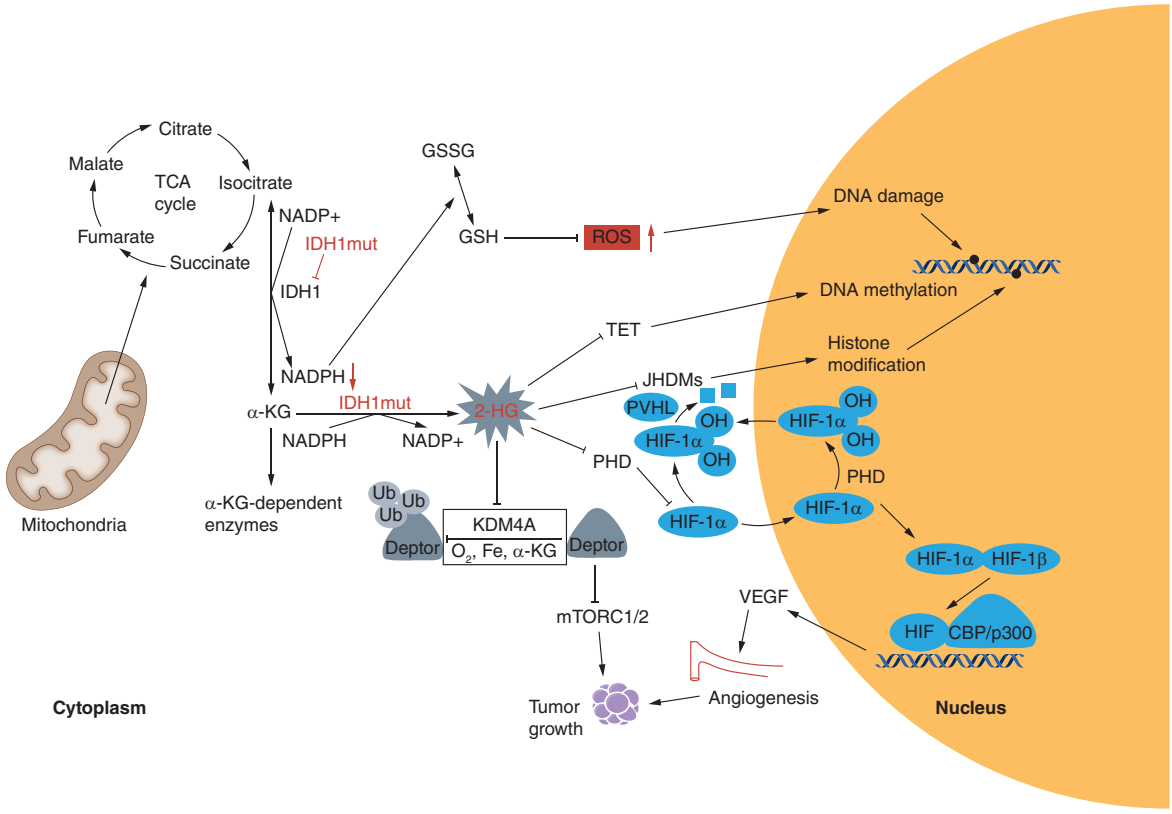

Figure 2. IDH1 mutants play a role in tumorigenesis. IDH1 mutations catalyze the production of 2-HG from α-KG and consume NADPH. α-KG is the substrate of a variety of dioxygenases (including JmjC domain-containing histone demethylase (JHDM)s, TET, PDH, KDM4A, etc.). Carcinogenic metabolite 2-HG inhibits the activity of several α-KG dependent dioxygenases. 1. TET: 2-HG can inhibit the activity of TET and lead to abnormal DNA methylation, which eventually leads to tumor. 2. JHDMs: 2-HG inhibits α-KG dependent histone demethylase, resulting in abnormal gene expression and ultimately tumorigenesis. 3. KDM4A: KDM4A stabilizes the endogenous negative regulator Deptor of mTOR by inhibiting the ubiquitination of mTOR, thereby inhibiting the activation of mTORC1 and mTORC2. Deptor can be rapidly degraded by 2-HG, leading to activation of MTORC1/2, thereby aiding the survival of cancer cells. 4. PHD: As an oxygen sensor, it regulates tissue oxygen levels and angiogenesis. 2-HG inhibits PHD activity, upregulates hypoxia-inducible factors-1α, activates downstream tumor-related pathways, and promotes tumor angiogenesis. In addition, reduced cytoplasmic NADPH levels further reduce GSH and thioredoxin levels, leading to elevated reactive oxygen species levels that further lead to DNA damage and promote tumorgenesis.
2-HG: 2-Hydroxyglutarate; α-KG: α-Ketoglutarate; GSH:Glutathione; IDH1mut: IDH1 mutation; JHDM: Jumonji-C domain-containing histone demethylase; JmjC: Jumonji-C; KDM4A: Lysine-specific demethylase 4; PDH: Prolyl-4-hydroxylase; ROS: Reactive oxygen species; TET: Ten-eleven translocation.

Glucose metabolism

IDH1 is essential for glucose metabolism. In normal human cells, pyruvate is converted to acetyl-CoA and enters the mitochondrial TCA cycle. However, the glucose metabolism of IDH1 mutant and IDH1 wild-type tumor cells is different [41]. In IDH1 wild-type tumors, pyruvate is metabolized to lactic acid. The IDH1 mutation decreases the activity of pyruvate dehydrogenase and the ability to produce lactic acid [44,45]. In IDH1 mutant glioma cells, the content of citric acid synthase and other metabolic enzymes of the TCA cycle increased [29]. Skp2, an E3 ubiquitin ligase, can degrade IDH1/2, which may reduce the stability of IDH1 protein [46]. Skp2 inhibition leads to increased IDH1 protein stability and shifts glucose metabolism from glycolysis to the TCA cycle in prostate cancer cells, thereby inhibiting glycolysis and tumorigenesis [6]. In addition, in primary glioblastoma multiforme (GBM), decreased IDH1 activity will lead to a decrease in the production of NADPH, reduced glutathione is consumed, and reactive oxygen species (ROS) levels increase [28]. Jiang *et al.* found that adaptation to anchoring independence requires fundamental changes in citrate metabolism, initiated by IDH1-dependent reducing carboxylation, which ultimately inhibits mitochondrial ROS. [47]. In the absence of IDH1, NADPH derived from pentose phosphate is also used to resist cytoplasmic ROS [47].

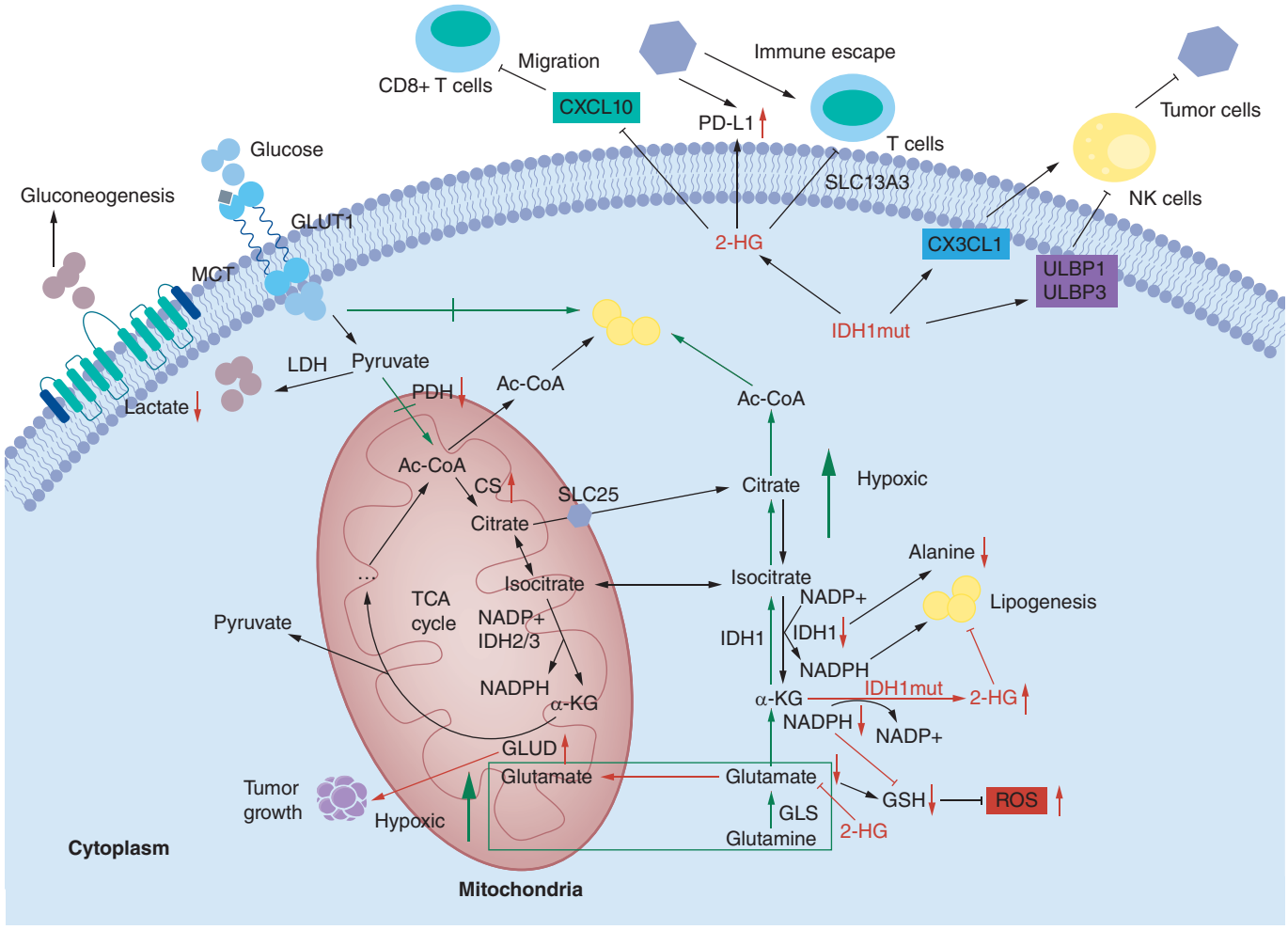

Figure 3. Effect of IDH1 changes on tumor metabolism and immunity under hypoxia. Pyruvate is metabolized to lactic acid in IDH1 wild-type tumors. Decreased IDH1 activity leads to reduced NADPH production, reduced glutathione consumption and increased reactive oxygen species levels. Glucose consumption increases and utilization of amino acids decreases. IDH1 mutations lead to decreased PDH activity and lactic acid production. Hypoxic microenvironment promotes glutamine to enter tricarboxylic acid cycle and participate in metabolism, making up for the loss of α-KG. IDH1-catalyzed NADPH and Ac-CoA are indispensable substrates for the synthesis of lipids. IDH1 mutations reduce α-KG and NADPH levels, ultimately reducing lipid synthesis. IDH1 deficiency impairs the production of amino acids such as alanine and α-KG dependent glucose. SLC25A1 can promote the excretion of citric acid from mitochondria to cytoplasm. 2-HG produced by IDH1 mutation can be taken up by nearby T cells via the SLC13A3 transporter and inhibit T-cell proliferation and activation. 2-HG reduces the expression of tumor-specific CD8+ cytotoxic T-lymphocyte-related genes, including type 1 chemokine CXCL10, which directly leads to the migration of CD8+ T-cell cut back. Inhibition of 2-HG caused anti-mIDH1 glioma immune memory, thereby increasing the expression level of PD-L1 on mIDH1-glioma cells. IDH-mutated glioma cells gain resistance to NK cells through epigenetic silencing receptor NKG2D ligands ULBP1 and ULBP3. IDH1 R132H mutation leads to increased expression of the chemokine CX3CL1, which promotes the recruitment of NK cells and inhibits tumorigenesis.
2-HG: 2-Hydroxyglutarate; α-KG: α-Ketoglutarate; GSH: Glutathione; IDH1mut: IDH1 mutation; PDH: Pyruvate dehydrogenase; ROS: Reactive oxygen species.

Amino acid metabolism

IDH1 is also essential for amino acid metabolism in tumor cells. HepG2 cells lacking IDH1 increased glucose consumption, increased alanine levels and decreased intracellular α-KG levels. IDH1 deficiency impairs amino acids such as alanine and α-KG-dependent glucose production [48]. In addition, although citric acid is produced in mitochondria, it is an important substrate for IDH1 biosynthesis in cytoplasm. As a mitochondrial citrate carrier, SLC25A1 is an important upstream molecule of IDH1. It can promote the excretion of citric acid from the mitochondria to the cytoplasm [49].

NADP+/NADPH can be regulated by IDH1 to protect cells from oxidative stress. IDH1 mutation may rely on the availability of cysteine in GSH to ensure antioxidant function [12]. In IDH1 mutant gliomas, the content of α-KG in the cells did not decrease significantly, but the content of 2-HG increased significantly. Currently, the tumor's hypoxic microenvironment promotes glutamine to enter the TCA cycle and participate in metabolism [50]. The glutamine pathway makes up for the loss of α-KG. This demonstrates that tumor cells are more likely to take up glutamine [51]. Glutaminase and glutamine dehydrogenase are enzymes that catalyze glutamate to α-KG. The increase of glutaminase can maintain the reaction from a-KG to D-2HG [28]. Research found that glutamate dehydrogenase 2 promotes the growth of IDH1R132H glioma [52]. In addition, inhibition of transaminases by 2-HG impairs redox homeostasis and glutamate biosynthesis in gliomas [53].

Lipid metabolism

IDH1 not only participates in oxidative phosphorylation metabolism but also plays an important role in the process of lipid synthesis. IDH1 catalyzes isocitrate to produce NADPH and α-KG. NADPH and acetyl-CoA are essential substrates for lipid synthesis. When tumor cells are hypoxic, IDH1 catalyzes lipid synthesis mediated by α-KG derived from glutamate, producing isocitrate, which can be catalyzed to produce citric acid, and citric acid is further decomposed to produce acetyl-CoA, thereby participating in lipid synthesis [13,20,33]. In addition, SREBP, as a transcriptional regulator, participates in the (*de novo*) synthesis of lipids [54].

Calvert *et al.* confirmed that wild-type IDH1 is overexpressed in glioblastoma, and inhibition of IDH1 activity can affect lipid production [6]. IDH1 mutations can also affect cell lipids synthesis and adversely affect the growth of mutant cells. In IDH1 mutant fibrosarcoma cells, D-2HG limits the lipogenesis involved in NADPH [55]. Mustafa *et al.* have found that IDH1 mutant glioblastoma cells have increased IDH2 enzyme activity, indicating that mutant cells may compensate for the adverse effects of IDH1 mutations through the IDH2 pathway [29]. This may explain why glioma cells rarely have both IDH1 and IDH2 mutations.

Regulation of IDH1 & related signal pathways

The expression of IDH1 is regulated by many mechanisms. Molecules such as CHOP, Nrf2, c-Myc, FoxO6 and SREBP play important roles in the expression of IDH1 (Figure 4).

CHOP

CHOP is involved in regulating cellular energy metabolism, proliferation and differentiation [56]. It plays an important role in the expression of IDH1. The expression of CHOP in melanoma cells increases when the endoplasmic reticulum is stressed, and CHOP binds C/EBPβ to form a heterodimer that regulates the IDH1 promoter region. IDH1 expression is upregulated, leading to HIF-1α degradation, thereby inhibiting the survival of melanoma cells [31].

Nrf2

Nrf2 is involved in a few proteins that regulate cell homeostasis, including antioxidant proteins, drug transporters and others. IDH1 mutant cells rely on the Nrf2 antioxidant pathway. IDH1 mutation changes the homeostasis of ROS in cancer cells and can rely on the Nrf2 antioxidant pathway to eliminate ROS [57]. The latest research shows that in IDH1 mutant cells, triptolide can regulate Nrf2 related pathways, inhibit glutathione synthesis, accumulate ROS and ultimately lead to the death of IDH1 mutant cancer cells due to oxidative stress [58].

c-Myc

The oncogene c-Myc plays an important role in regulating glycolysis under normoxic and hypoxic conditions in tumor cells, usually through the key factor HIF-1α [59]. This process is regulated by the *IDH1-AS1* gene of long noncoding RNA located in the cytoplasm. The signal axis c-Myc-(IDH1-AS1)-α-KG/ROS-HIF1α activates the Warburg effect under normoxia [27].

HuR

HuR/ELAVL1 has been reported to be closely related to the occurrence of various cancers. HuR can regulate mutant and wild-type IDH1 in IDH1-mutant cancers [60]. Zarei *et al.* demonstrated that IDH1 is the only antioxidant enzyme regulated by HuR, and pancreatic ductal adenocarcinoma cells lacking HuR are also difficult

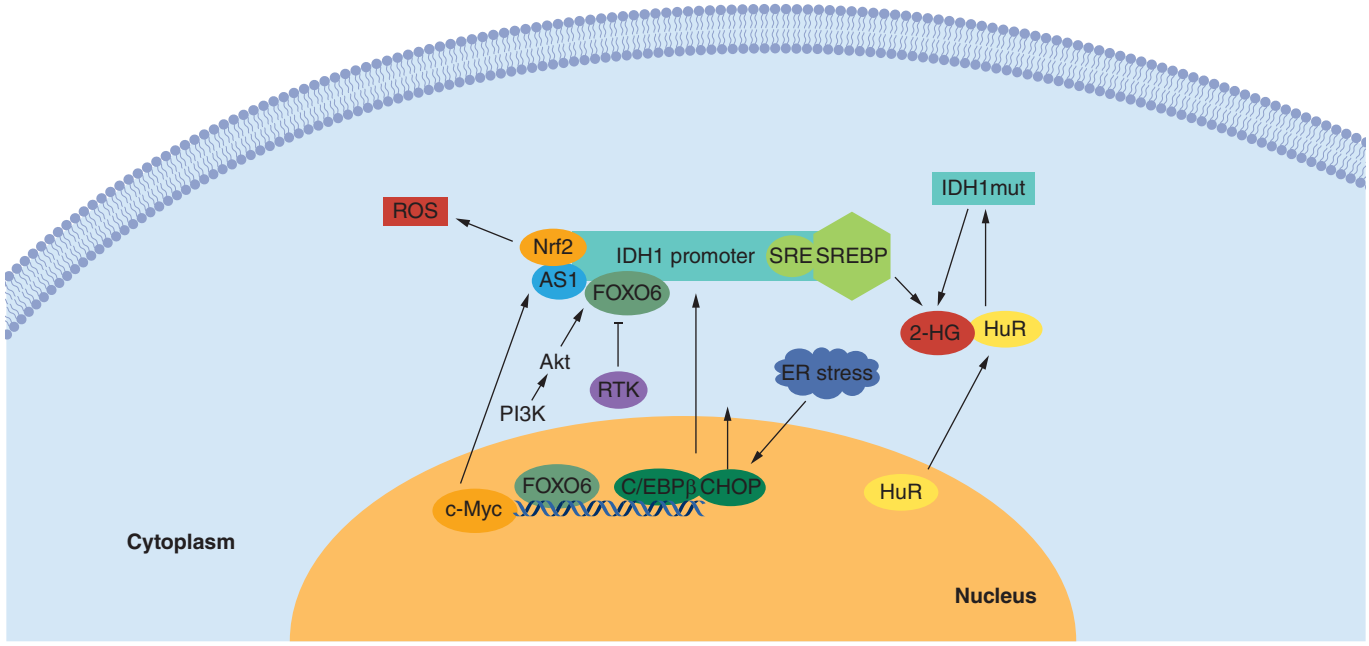

Figure 4. The regulatory mechanism of IDH1. Molecules such as CHOP, Nrf2, c-Myc, FoxO6 and sterol-regulatory element binding proteins play important roles in the expression of IDH1.
2-HG: 2-Hydroxyglutarate; ER stress: Endoplasmic reticulumstress; IDH1mut: IDH1 mutation; ROS: Reactive oxygen species.

to transplant successfully in immunodeficient mice. In contrast, the overexpression of IDH1 in pancreatic ductal adenocarcinoma cells can cause tumors to grow again [61].

IDH1 related signal pathways

The activation of the PI3K/AKT/mTOR signaling pathway is closely related to tumor migration and invasion. The induced activation of IDH1 also depends on the signal axis of receptor tyrosine kinase (RTK)-PI3K-Akt-FoxO6 [6]. FoxO6 binds to the IDH1 intron consensus binding site. FoxO6 is inhibited by RTK, and IDH1 expression can be induced [6]. Carbonneau *et al.* proposed that mutant IDH1 produces 2-HG, which inhibits the α-KG-dependent enzyme lysine-specific demethylase 4 to activate the process of mTOR, thereby inhibiting the growth of tumor cells [62].

As a coenzyme of dehydrogenase, NAD^+ is indispensable for tumor cell metabolism. Tateishi *et al.* found that IDH1 mutants inhibit tumor growth by reducing NAD^+ levels and showing sensitivity to NAD^+ depletion [63]. IDH1 mutant tumors downregulate nicotinamide phosphoribosyltransferase in the process of NAD^+ synthesis and reduce the level of NAD^+. The decrease of NAD^+ level activates Adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK), which triggers autophagy and ultimately leads to tumor cell death [63].

TGF-β is a multifunctional cytokine. IDH1 can affect TGF-β signaling through the TGFBR-IDH1-Cav1 axis, which in turn affects tumor development [64]. In addition, SREBP also can directly bind specifically to the SRE sequence of the IDH1 promoter, activate the expression of IDH1 and influence 2-HG production in IDH1 mutant cells and lipid synthesis in IDH1 wild-type cells [54].

IDH1 & tumor immunity

The occurrence and development of tumors require a suitable tumor microenvironment, which is composed of many cell types, such as tumor cells, fibroblasts, vascular endothelial cells and various immune cells [65]. The mutated IDH1 in tumors is related to the decrease of immune cells (T cells, B cells, macrophages, etc.) and may evade NK cell immune surveillance by downregulating the expression of related ligands [66,67]. Understanding the

specific mechanism of IDH1 in tumor immunity may help to develop new drugs for immunotherapy against mutated IDH1 tumors (Figure 3).

$CD4^+$/$CD8^+$T cells

IDH1 mutation contributes to the progression of malignant tumors of the T-cell lineage and may change the metabolic characteristics of malignant T cells [66]. 2-HG produced by IDH1 mutation can be ingested by nearby T cells via the SLC13A3 and inhibit T-cell activation [37]. In IDH1 mutant glioma, 2-HG suppresses the human immune system and promotes the immune escape of the tumor [68]. 2-HG reduces the effect of various specific treatments against mutant IDH1 (such as specific vaccines and IDH1 mutation inhibitors) on tumor treatment [37]. In addition, inhibition of 2-HG caused anti-mIDH1 glioma immune memory, thereby increasing the expression level of PD-L1 on mIDH1-glioma cells [69]. It also reduces depletion of T cells and promotes the production of memory $CD8^+$ T cells [68]. Antitumor activity of $CD8^+$ T cells requires a sufficient supply of glutamine. Glutamine metabolism disorders can lead to T-cell depletion [70]. 2-HG reduces the expression of tumor-specific $CD8^+$ cytotoxic T-lymphocyte-related genes, including IFN-γ-induced chemokines such as type 1 chemokine CXCL10, which directly leads to the migration of $CD8^+$ T-cell cut back [71]. $CD4^+$ T cells may respond to class II-restricted new epitopes containing IDH1 R132H mutations. IDH1 mutant glioma may attract IDH1-specific mutant $CD4^+$ T cells. IDH1 (R132H) as a tumor-specific antigen is a potential immunotherapy target [71].

Treg cells

Treg cells are also present in the tumor microenvironment [64]. The inhibitory effect of Treg on antitumor immunity of human glioma is related to the tumor microenvironment. 2-HG produced by IDH1 mutations induces metabolic changes that affect Tregs differentiation. D-2-HG can increase mTOR activity and interfere with HIF-1α stability, leading to metabolic bias toward oxidative phosphorylation, increased Treg frequency and decreased T-helper 17 polarization [72]. Because Treg expression is lower in IDH1-mutated tumors than in wild-type tumors, treatment with Tregs may be more appropriate to modulate IDH1-wild-type tumors [73].

NK cells

NK cells are a type of lymphocyte that can nonspecifically recognize and kill tumor cells. IDH mutated glioma cells gain resistance to NK cells by epigenetic interference with the receptor NKG2D ligands ULBP1 and ULBP3, which provides a new therapeutic option for NK-cell-mediated immune monitoring in IDH mutated glioma patients [67]. In addition, IDH1 R132H mutation leads to increased expression of the chemokine CX3CL1, which promotes the recruitment of NK cells and inhibits tumorigenesis [74].

Tumor-associated macrophages

2-HG produced by IDH1 mutation may also affect macrophages in the tumor microenvironment [75]. The effect of macrophages on tumor development mainly depends on the secreted pro-angiogenic factors (VEGF, CSF, MMPs etc.). Studies have found that the 1p/19q co-deletion status affects the degree of tumor-associated macrophage (TAM) infiltration of IDH-mutated gliomas. The specific mechanism is jointly mediated by macrophage CSF and TGFβ1 [75]. Glioblastoma with dense $CD204^+$TAMs and several $CD4^+$TILs is associated with wild-type IDH1, suggesting that TAMs mask tumor cells and inhibit tumor glycoside function in T cells through an immunomodulatory mechanism [76]. IDH1 mutant promotes the phagocytosis of microglia and macrophages in gliomas by downregulating ICAM-1. In IDH1 wild-type glioma cells, ICAM-1 silencing increased the antitumor function of TAMs and inhibited tumor growth [77].

IDH1 & tumor treatment

Given the important role of IDH1 mutations in tumor development, targeted development of corresponding therapies will provide new hope for the treatment of patients with IDH1 mutations. Many IDH1 inhibitors, vaccines and immune checkpoint inhibitors have also entered clinical trials (Table 2).

IDH1 inhibitors

IDH1 inhibitors can inhibit IDH1 mutations and reduce 2-HG to normal levels, thereby exerting antitumor effects. The US FDA has approved the first mIDH1 inhibitor ivosidenib (AG-120) for the treatment of acute myeloid leukemia, opening a prelude to IDH1-targeted mutation inhibitors [78]. Pusch *et al.* developed BAY 1436032, an

Table 2. IDH1 inhibitors and vaccines in clinical trials.

Drug	Target	Cancer	Clinical trial number
Ivosidenib (AG-120)	IDH1R132H	Low-grade glioma, Hematologic malignancies, Cholangiocarcinoma	NCT02073994 NCT04056910 NCT04195555
BAY1436032	IDH1R132H	Advanced malignancies	NCT02746081 NCT03127735
IDH-305	IDH1R132H	Hematological malignancies	NCT02381886
Olutasidenib (FT-2102)	IDH1R132	Acute myelocytic leukemia	NCT02719574
Vorasidenib (AG-881)	IDH1/IDH2	Hematological malignancies Low-grade glioma Some solid tumors	NCT02492737 NCT02481154 NCT03343197
NOA-16 (vaccine)	IDH1R132H	Glioma	NCT02193347 NCT02771301 NCT03893903
IDH1R132H-DC (vaccine)	IDH1R132H	Glioma	NCT02771301

IDH: Isocitrate dehydrogenase.

inhibitor targeting tumors with IDH1R132 mutations, which can promote the proliferation of tumor-infiltrating CD4+ T cells and significantly reduce the level of 2-HG [79]. In the IDH1-MUT glioma mouse, treatment with IDH-C35 (IDH1-R132H inhibitors) enhances the immunotherapy effect and promotes T-cell infiltration [71].

Immune targeted therapy

The mutated IDH1-R132H protein contains a new immunogenicity epitope that has been used to develop vaccines against this mutated enzyme. Studies have shown that the IDH1R132H specific peptide vaccine can slow the growth of IDH1R132H mutant glioma [80]. In addition, the combination of specific vaccines with IDH1 inhibitors may provide better results. For example, in mice transplanted with GL261 glioma cells expressing IDH1-R132H, the combination of IDH1-inhibitor and peptide-based vaccine can significantly improve patient survival compared with vaccine alone [71]. Immune checkpoint inhibitors are effective in several malignancies without IDH1 mutations, but their immune efficacy against IDH1 mutated tumors remains unclear. However, 2-HG can inhibit the expression of PD-L1, suggesting that the future treatment of IDH mutant gliomas with immune checkpoint inhibitors alone is promising [69].

Metabolism targeted therapy

Currently, there are no drugs that target to block IDH1 mutations that cause IDH1 metabolic abnormalities or restore IDH1 normal metabolism, but the unique weaknesses of tumors that target IDH1-mutated may contribute to the development of therapies for IDH1-mutated cancers [63].

Conclusion

IDH1 plays a key role in many metabolic processes of cells and is also a key source of NADPH involved in the reduction process in the body. In recent years, it has been found that IDH1 is associated with a variety of human tumors and plays an important role in tumor metabolism and tumor immunity. wild-type IDH1 can promote or inhibit the development of some tumors. The mutant IDH1 plays an important role in the development of tumors, especially glioma and AML. IDH1 mutations or expression changes are closely related to the occurrence and development of tumors. IDH1 is considered to be an attractive target for cancer therapy.

Future perspective

As a potential clinical target, IDH1 may have significant implications for the evaluation and treatment of the disease. In future studies, researchers should continue to explore the roles of IDH1 in more diseases and whether it can be used as a target for the treatment of the disease, offering hope to more patients.

Currently, although drugs targeting IDH1 mutations, such as IDH1 mutation inhibitors and immune-targeted drugs, have been used clinically, no new drugs have been launched for the target of wild-type IDH1. Therefore, we believe that future research directions in this field will focus on metabolic replacement strategies for IDH1-mutant tumors and the development of therapeutic strategies based on IDH1 wild-type tumors. We also believe that more

IDH1 inhibitors and immune vaccines will be developed. These will bring new hope for the clinical treatment of patients with IDH1 mutations or altered expression.

Executive summary

Introduction
- IDH1 is a key metabolic enzyme for cellular respiration in the tricarboxylic acid (TCA) cycle.

Structure & function of IDH1
- The structure of IDH1 is summarized. IDH1 can convert isocitrate into α-ketoglutarate and generate NADPH. The reduction of IDH1 may affect dioxygenase activity and damage the body's detoxification mechanism.

IDH1 & malignant tumors
- IDH1 mutation or activity change play a role in tumorigenesis. Studies have shown that IDH1 is low expressed in renal cell carcinoma and IDH1 upregulation is closely related to tumor metastasis in IDH1 non-mutated glioblastoma. IDH1 mutations can lead to the occurrence of various solid tumors.

IDH1 & tumor metabolism
- As a key enzyme in metabolism, IDH1 causes a series of changes in the metabolic pathway of tumor cells – including glucose metabolism, amino acid metabolism and lipid metabolism – and further influence the progress of the tumor.

Regulation of IDH1 & related signal pathways
- The roles of molecules such as CHOP, Nrf2, c-Myc, FoxO6 and SREBP in the expression of IDH1 are summarized in this review.

IDH1 & tumor immunity
- The specific mechanism of IDH1 in tumor immunity is summarized.

IDH1 & tumor treatment
- IDH1 mutant inhibitors or vaccines may treat IDH1 mutations.

Conclusion
- The main purpose of this review is to provide a better understanding of the relationship between IDH1 and tumor development.

Future perspective
- Researchers should continue to explore the roles of IDH1 in more diseases and whether it can be used as a target for the treatment of the disease, bringing hope to more patients.

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- **IDH1 inhibitors can inhibit IDH1 mutations and reduce 2-HG to normal levels, thereby exerting antitumor effects**

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